Non-Exercise Activity Thermogenesis
The Crouching Tiger Hidden Dragon of Societal Weight Gain

James A. Levine, Mark W. Vander Weg, James O. Hill, Robert C. Klesges, Margo Denke

Abstract—Non-exercise activity thermogenesis (NEAT) is the energy expenditure of all physical activities other than volitional sporting-like exercise. NEAT includes all the activities that render us vibrant, unique, and independent beings such as working, playing, and dancing. Because people of the same weight have markedly variable activity levels, it is not surprising that NEAT varies substantially between people by 2000 kcal per day. Evidence suggests that low NEAT may occur in obesity but in a very specific fashion. Obese individuals appear to exhibit an innate tendency to be seated for 2.5 hours per day more than sedentary lean counterparts. If obese individuals were to adopt the lean “NEAT-o-type,” they could potentially expend an additional 350 kcal per day. Obesity was rare a century ago and the human genotype has not changed over that time. Thus, the obesity epidemic may reflect the emergence of a chair-enticing environment to which those with an innate tendency to sit, did so, and became obese. To reverse obesity, we need to develop individual strategies to promote standing and ambulating time by 2.5 hours per day and also re-engineer our work, school, and home environments to render active living the option of choice. (Arterioscler Thromb Vasc Biol. 2006;26:000-000.)

Key Words: non-exercise activity thermogenesis ▪ physical activity ▪ energy expenditure ▪ obesity ▪ malnutrition

The first law of thermodynamics is the thermodynamic expression of the principle of the conservation of energy and states that when energy is added to a system, it is either stored or used to perform work. Applying this physical law to living entities, such as animals, provides us with the conclusion that when total energy intake is greater than energy expenditure, excess energy will be stored as body fat. The physiological states of overweight and obese are a consequence of cumulative excesses in caloric intake.

A pandemic of obesity has spread from the US to Europe and is now emerging in middle and even low-income countries. Overweight and obesity are preventable causes of death and many comorbidities including type II diabetes, hypertension, stroke, cholelithiasis, degenerative arthritis, sleep apnea, and cancer. With the prevalence of overweight and obesity increasing, the urgency to understand why humans are gaining weight has intensified.

Understanding the specific details of this pandemic is important. Most articles reporting the rise in prevalence of overweight and obesity use body mass index cutpoints; all have reported striking increases in prevalence. Far more profound, however, is the changes in average heights and weights across all ages. For example, since the 1970s, whereas the average height of American men and women has increased, the average weight has increased 25 pounds. It is tempting to attribute the increase in average weight to changes in population demographics, ie, “middle age spread,” from aging baby boomers. However, no category of individuals has escaped without weight gain, as reflected in the trend of mean weight for 2 age categories for both men and women (Table 1). Similar trends can be seen in data from children and adolescents. Thus, it is not simply that more people are overweight or obese, the entire population is gaining weight.

There has been controversy as to whether increases energy intake has been associated with the obesity epidemic. For example, since the 1980s obesity rates have doubled in Britain yet energy intake appears to have decreased. The NANES surveys in the United States are difficult to interpret because the recall method used to examine food intake changed between survey II and survey III. Energy intake increased between survey II and survey III but did not increase between survey I and II and did not increase between survey III and IV. This suggests that the increases noted between surveys II and III may have been methodological. Furthermore, looking at these data as a whole, it does not appear that body mass index tracks energy intake (Figure 1). The problem is that energy intake assessments of this nature are associated with measurement errors of up to 100%, and so we cannot be sure that dietary intake has remained unchanged with the emergence of obesity.

In the absence of firm data that positively associate increased energy intake with obesity, the role of energy expenditure in human energy balance has come under greater scrutiny. Classically, there are 3 components of total daily
energy expenditure (TDEE) in humans (Figure 2): basal metabolic rate (BMR), thermic effect of food (TEF), and activity thermogenesis (AT). BMR is the energy expenditure (EE) when a postabsorptive individual is laying at rest. BMR can be measured with errors of <1% generally using a high-precision, validated, indirect calorimeter.6 In sedentary individuals, BMR accounts for \( \approx 60\% \) of TDEE and can be well-predicted by lean body mass (\( \approx 80\% \) of the variance) within and across species.7,8 TEF is the increase in EE associated with the digestion, absorption, and storage of food and accounts for \( \approx 6\% \) to 12\% of TDEE. TEF can be measured by making repeated measurements of energy expenditure after a meal, using an indirect calorimeter; it accounts for \( \approx 11\% \) of TDEE.6 Activity thermogenesis is typically derived by summing BMR plus TEF and subtracting this product from TDEE. Physical activity level (PAL) is frequently calculated also and is TDEE/BMR. PAL is a useful metric because most investigators do not measure TEF and by correcting TDEE for BMR, an implicit correction is made for basal (resting) energy needs and body size.

Variation in Daily EE
When trying to understand whether EE might be important in obesity and body weight modulation, we might first examine the variability in total daily energy expenditure. If TDEE is very similar between different humans, then its modulation is unlikely to crucial.4 Thus, the first question then is, how variable is TDEE?

Doubly labeled water provides a precise measurements of TDEE, with an accuracy of \( \pm 5\% \). Several studies have performed 2 doubly labeled water measurements of TDEE when weight, activity, and physiological state were maintained. The estimated coefficient of variation between measurements is \( \approx 9\% \).9,10 Limiting analysis to measurements by doubly labeled water, TDEE varies enormously among individuals11 (Figure 3). Male soldiers in the field may have 3-fold greater transesophageal echocardiography (TEE) than the incapacitated elderly.11 The marked variance in TDEE is even greater when data from non-industrialized countries is considered when daily energy requirements of normal living vary 2.5-fold.12,13

In summary, for 2 adults of similar size TDEE can vary by as much as 2000 kcal per day. As noted, BMR is largely (80\%) accounted for by body size and TEF is a small component of TDEE (6\% to 12\%), so the variance in TDEE between people of similar size can only be explained by variance in AT.

AT comprises 2 definable components. The first is the EE of exercise and the remainder of AT is non-exercise activity thermogenesis (NEAT). Exercise is most easily defined as the purposeful physical activity undertaken for health (eg, sport, visiting the gym or club) and is defined in the Merriam-Webster Dictionary as “bodily exertion for the sake of developing and maintaining physical fitness.”14 We do not review sporting-like exercise here.15 However, the majority of world-dwellers do not participate in exercise as so defined;
hence, for them, exercise activity thermogenesis is zero. Even for the majority of "exercisers" who participate in exercise for <2 hours per week, exercise accounts for an average energy expenditure of ≈100 kcal per day. Thus, for the majority of people, it is not variable exercise levels but rather the variance in NEAT that accounts for most of the variability in AT. So, is it possible that NEAT could be highly variable?

NEAT

NEAT is the energy expenditure of all physical activities other than volitional sporting-like exercise. NEAT includes all those activities that render us vibrant, unique, and independent beings such as going to work, playing guitar, toe-tapping, and dancing. NEAT is expended every day and may be easier to conceptualize by considering activities during work and leisure hours.

Variance in Occupational NEAT

Most of the variance in NEAT between people is associated with differences in occupation. Here, data are most commonly expressed as PAL values (noting that the majority of people do not exercise regularly). PAL is TDEE/BMR and represents a correction of TDEE for body size. PAL values vary substantially between occupations (Table 2). To illustrate this point, consider a sedentary office worker with total daily energy requirements of 2400 kcal per day, a BMR of 1500 kcal per day, and a PAL of 1.6. If he/she were to change occupation to achieve a PAL of 2.4, for example by now working in agriculture or construction, NEAT could be increased by 1200 kcal per day. Thus, occupation has a major influence on NEAT and TDEE.

Variance in Leisure-Time NEAT

The energy expended in a variety of activities is shown in Figure 4. Consider, again, the same office worker. Argue that he/she returns home from work, by car, at 5 pm. From then until bedtime at 11:00pm the primary activity is to operate the television remote control in a semi-recumbent position. For these 6 hours, the average EE above resting would be ≈8% and the NEAT will thus be ≈30 kcal for the evening [0.08*1500BMR*(6/24) hours]. Now imagine he/she becomes aware of the unpainted bedroom, the weeds growing in the yard, and the possibility of cycling to work. The person then decides to undertake these tasks. The increase in energy expenditure would be equivalent to walking 1 to 2 mph for the same period of leisure time (5:00 to 11:00PM). NEAT then increases to 750 to 1125 kcal for the evening [2 or 3*1500BMR*(6/24) hours]. Thus, for this hypothetical office worker, the variance in leisure-time NEAT has the potential of impacting TDEE by up to 1000 kcal per day.

The potential variance in NEAT is therefore substantial and can vary for a given person by as much as 2000 kcal per day. NEAT could therefore be important in obesity.

NEAT in Weight Gain and Obesity

In humans, manipulation of energy balance is associated with changes in NEAT. In 1 study, 12 pairs of twins were overfed by 1000 kcal per day. There was 4-fold variation in weight gain, which by definition must have reflected substantial variance in energy expenditure. Because the changes in energy expenditure were not accounted for by changes in basal metabolic rate, indirectly changes is NEAT were implicated. Interestingly, twinness accounted for a substantial minority of the inter-individual variance in weight gain suggesting that NEAT is both under environmental and biological/genetic influences. With positive energy balance, NEAT increases. Moreover, the change in NEAT is predictive of fat gain. Those with overfeeding increase their NEAT the most and gain the least fat. Those with overfeeding

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TABLE 2. Lifestyle-Based Prediction of PAL values (11)

<table>
<thead>
<tr>
<th>Occupation Type</th>
<th>PAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair-bound or bed-bound</td>
<td>1.2</td>
</tr>
<tr>
<td>Seated work with no option of moving around and</td>
<td>1.4–1.5</td>
</tr>
<tr>
<td>little or no strenuous leisure activity</td>
<td></td>
</tr>
<tr>
<td>Seated work with discretion and requirement to move</td>
<td>1.6–1.7</td>
</tr>
<tr>
<td>around but little or no strenuous leisure activity</td>
<td></td>
</tr>
<tr>
<td>Standing work (eg, housewife, shop assistant)</td>
<td>1.8–1.9</td>
</tr>
<tr>
<td>Strenuous work or highly active leisure</td>
<td>2.0–2.4</td>
</tr>
</tbody>
</table>
do not increase their NEAT and gain the most fat. It was therefore tenable to examine the role of NEAT in obesity.

The role of NEAT in obesity was recently highlighted by the observation that lean sedentary people are standing and ambulatory for 152 minutes longer per day than obese participants. These observations were made using microsensors that subjects wore under their clothes and allowed body postures and movements to be accurately measured every half-second per day. Obese participants were seated for 164 minutes per day more than lean participants (Figure 5). If the obese subjects adopted the same posture allocation as the lean subjects, they might expend an additional 350 kcal per day because of the energy cost of standing/ambulating. It is interesting to note that the magnitude of this defect almost identically matched that identified in Schoeller’s analysis of the formal exercise level that obese people need to adopt to promote negative energy balance and weight loss. Thus, NEAT and specifically standing/ambulating time are of substantial energetic importance in obesity.

Thus, NEAT varies by up to 2000 kcal per day between different people. Modulation of NEAT appears to be important in weight gain, but more importantly individuals with obesity show low NEAT. Specifically, obese individuals have an innate predisposition to be seated for 2.5 hours per day more than sedentary lean counterparts. Because the human genetic code has not changed in 50 years and obesity has become epidemic, obesity may, in part, represent a state of enhanced responsiveness to the environmental cues to be seated. It is therefore necessary to review the environmental factors that are associated with low NEAT.

Environmental Factors That Impact NEAT
There are a wide variety of geocentric environmental factors that impact NEAT.

The Concrete Urban Environment and Mechanization
Sedentariness and a sedentary-promoting environment are pervasive features of the 21st century in high- and middle-income countries. Physical activity levels have declined as individuals move from agricultural communities to urban environments and as industrialization is more commonplace. Sedentary cues are unmistakable in developed countries often through services designed to optimize convenience and throughput at the expense of locomotion. Examples include drive-through restaurants and banks, televisions, escalators, motorized walkways, and clothes washing machines.

Schools may be built beyond walking distance of the community served, suburbs are built without sidewalks, city streets are considered to be unsafe for leisure-time walking, or playgrounds are unsafe for children to play in. A comparison between the energetic costs of mechanized tasks with the same tasks performed manually as would have occurred a century ago indicates that the energy cost to mechanization is approximately 111 kcal per day. This agrees with an independent estimate of the cost of mechanization. It is worth noting also that sales of labor-saving devices track with obesity rates in the United States, whereas food intake data do not (Figure 1). Urbanization and mechanization are likely to have dramatically impacted NEAT.

Gender
Although gender is biologically determined, there are gender-specific environmental cues that impact NEAT. Overall, adult men and women in the United States report similar levels of total physical activity although women are becoming more active. In other countries, such as Canada, England, and Australia, men tend to be more active than women. In children, there are consistent gender differences, with boys being more active than girls. Gender may also influence physical activity in more subtle ways. For example, society and culture may dictate that a woman work both in the public and the home. Where this occurs in agricultural communities, women’s energy needs were found to be 30% greater than predicted. In agricultural communities, women’s energy needs were found to be 30% greater than predicted.

There are no data of NEAT for women with similar societal-derived roles in high-income countries. However, there are likely to be environmental drives on NEAT that affect genders differently in many communities.

Education
Groups with more education consistently report more leisure time physical activity than groups with less education. In the United States, high education groups are about 2- to 3-times more likely to be active than low-education groups. This contrasts with low-income countries, where child labor is commonplace. In this situation, poverty is predictive of greater child labor and the most impoverished children thereby have the greatest NEAT levels.

Seasonal Variations in Physical Activity
Limited data are available regarding differences in NEAT during different seasons. Who volitionally walks to work in the rain? Data from Canada suggest wide differences in time...
spent in physical activity because of season. Time spent in activity was twice as high during the summer months compared with winter months. Common sense dictates and data confirm that occupation-associated NEAT is affected by season in agricultural communities where workloads vary cyclically.

It is self-evident that environmental factors impact NEAT (consider the comfort of chair you are sitting on as you read this), although there are few data that quantify these effects (or distinguish them from purposeful exercise). Regardless of these limitations, data strongly support the thesis that environmental factors promote sedentariness.

Conceptual Consideration Regarding NEAT-Enhanced Living

The data suggest that an increase in standing/ambulating time of 2.5 hours per day would convert the obese NEAT-o-type to the lean NEAT-o-type. Thus, if an obese woman stands/ambulates for 350 minutes per day on average, her goal would become to stand/ambulate for 500 minutes per day. Understanding that people are awake for 16 hours per day, it is clear that increasing standing time by 2.5 hours per day is challenging. Currently, there is little information available regarding how best to increase NEAT and so we need to examine existing infrastructures and contemplate new approaches. To achieve these goals, we first discuss individual NEAT-enhancing strategies. However, we also argue that because environmental influences have provided the overwhelming cues to sit, we should examine novel approaches to re-engineer our environment to promote standing and ambulating.

Strategies to Promote Individual NEAT

Behavioral economic theory provides a useful framework for how personalized interventions for increasing NEAT might be conceptualized and developed. As applied to NEAT, behavioral economic theory is concerned with how people make decisions about how they choose to allocate their time from among their numerous activity options. Issues include: (1) why, when given a choice, do people typically choose sedentary activities instead of more active ones?; (2) under what conditions will people allocate their time differently?; and (3) how can the environment and contingencies on behavior influence so that people select standing/ambulating behaviors as opposed to sedentary behaviors?

Several key principals based on behavioral economic theory can guide NEAT-based intervention for increasing standing/ambulating time. First, choice between activity alternatives is based in part on their behavioral “cost.” This refers to the behavioral cost associated with a given activity (eg, how hard a person will have to “work” to gain access to an activity). Not surprisingly, people are much more likely to choose activities that are more accessible such as an office-based activity program that does not require changing clothes. Second, choice among various activities depends in part on available alternatives. It is possible to shift a person’s choice of behaviors by providing them with access to a competing behavior that is highly valued (eg, a person may prefer to surf the Internet while seated when her standing/ambulating options are limited to things that dislikes such as a gym visit). However, if given access to an activity she really likes (eg, walking with a friend), she may choose to be active instead of Internet-surfing. Third, it is important to provide individuals with choice. Forcing an individual to choose a specific activity (eg, an exercise bike at X intensity for Y minutes, Z days per week, or an obligatory workplace exercise program) is likely to have the opposite of the intended effect; people view that activity as less reinforcing and select it less frequently when given free choice. Fourth, choice among activities depends, in part, on the delay between selecting the behavior and the outcome. Many sedentary behaviors that people enjoy have immediately reinforced consequences, whereas the health and fitness benefits of standing/ambulating may take longer to accrue. Thus, it is important to select standing/ambulating behaviors that are pleasing (eg, walk-and-talk or walk while listening to music).

These theoretical concepts can be converted into specific behavioral strategies:

Self-Monitoring and Feedback of Participants’ Behavior Choices

To increase an individual’s awareness of his or her own behavior, it is important for patients to gain the habit of looking and responding to their intervention and the associated target behaviors. There are several methods that patients can use to chart their progress with respect to NEAT interventions. Self-charting, for example, is widely used by our patients, such as by using a check list attached to the fridge. Pedometers can sometimes be useful for self-monitoring progress in a walking program, which is the commonest activity program selected by patients. However, the accuracy of commercially available pedometers is ~50% with equally poor precision, and so their use should not be overly promoted. Several automated approaches are applicable such as e-mail, PDAs, and electronic telephone messaging. Time spent on sedentary behaviors that might be targeted for reduction (eg, television watching, playing computer games) also should be assessed as part of the self-monitoring process.

Modify Specific Seated Behaviors so That They Can Be Performed While Standing

For example, if subjects feel that they “must” watch a certain amount of television, then they can choose to do so only while standing/pacing (although it might be preferable to limit television viewing).

Use of Sedentary Activities to Reinforce Physically Active Behaviors

For example, if subjects like to play computer games, a contingency management approach can be adopted so that they only use the computer (recreationally) after they have met their standing goals for the day. This approach has proven effective in children.

Identification of Behavioral “Substitutes” for the More Sedentary Behaviors That Require Sitting

This involves having participants select from among various different activities that they enjoy that would serve to “replace” sedentary behaviors.
Identify and Problem-Solving Barriers to Standing/Ambulating

Different factors can obstruct a person from increasing their standing/ambulating. Barriers such as fatigue, pain, work demands, depressed mood, social pressures, and weather need to be anticipated and addressed a priori.

Goal Setting/Gradual Behavior Change

Although the final behavioral goal may be well-defined (eg, baseline standing/ambulating time + 2.5 hours per day), and although the behavior change may not seem complex, an increase in standing/ambulating time of 2.5 hours per day is daunting and challenging to many obese people. Subject-specific targets need to be set where the goal is tenable.

Stimulus Control With Work and Home

From a behavioral economics perspective, the goal is to adopt approaches that will make standing and other active behaviors more accessible and sedentary behaviors less accessible (and therefore more “costly”), eg, moving the television out of the living room.

Presence of Trained and Motivated Team

There is a need to devise straightforward and readily disseminated approaches to behavioral modification that allow cohesive training of the intervention team in the health care setting, workplace, or school.

Incentives

Subjects like to receive rewards beyond continuous positive reinforcement and knowing that they are likely to be receiving an intervention that could help with health and potentially with weight loss.

When one reviews the 119 federal steps that encourage personal change with respect to weight loss, 61 of 119 recommendations focus on NEAT-enhancing activities (http://www.smallstep.gov/sm_steps/sm_steps_index.html). Thus, by selecting activities of choice and applying well-tested behavioral concepts a person can increase their NEAT in theory. The crucial next step is to examine whether these concepts can be translated into increased NEAT, negative energy balance, and weight loss. Studies are urgently needed.

Potential Environmental Strategies to Promote NEAT

There are 4 reasons to examine environmental re-engineering to promote NEAT despite the substantial investment in effort and cost. First, over the past century environmental cues have been so overwhelming that ambulatory individuals have been seduced to sit. Therefore, we need to redesign the environment itself to reverse this effect. Second, the NEAT deficit represents 2.5 hours of standing and ambulating per day. For a person to increase their standing/ambulating time to this degree, their environment will need to be activity-enticing or at least NEAT-permissive; therefore, it is logical to scrutinize the environment per se. Third, the fiscal cost of excess body weight and obesity is sufficiently great that effective measures to prevent and treat obesity are likely to be cost-effective for adults and children. In the United States alone, obesity-related medical expenditures in 2003 were ~$75 billion. Thus, it is tenable to contemplate environmental engineering as a fiscal investment. Finally, the health impact of overweight and obesity is overwhelming both for individuals and societies. In the United States poor diet and physical inactivity are associated with 400 000 deaths per year and obesity is emerging as a major health problem in middle-income and even low-income countries. Hence from a public health perspective, environmental re-engineering is likely to impact a sufficient proportion of the population to make it worthwhile.

Overall, the magnitude of the problem of overweight and obesity necessitates a response of matching intensity and resolve. We concur with the call for a “moratorium on the chair” and suggest that it is now time to fundamentally redesign our environments so that active living is the norm. At present, there is not body of knowledge to best define how to achieve these goals and so we speculate as to what re-engineered environments might entail.

The predominant factor that predicts the variability in NEAT is occupation, and we wonder whether work and school environments can be re-engineered to promote NEAT? In adults, because computer-based occupations are prevalent in industrialized and emerging economies and are projected to account for a greater segment of the workforce, a NEAT-enhancing office environment could be developed. Here office workers interact with computers in an environment that allows walking, should the employee choose. An employee can choose to remain seated throughout the workday too. The reason that this is so energetically potent can be discerned by reviewing existing data (Figure 2). When a person walks at 1 mph, they double their energy expenditure so that a 70-kg person would expend an extra 100 kcal per hour. Thus, even if a person “walked and worked” for half of every work day, they would expend an additional 400 kcal per day and exceed the NEAT deficit in obesity. Negative energy balance of this magnitude would be associated with >30 pounds of weight loss per year. Such dramatic environmental re-engineering is interestingly less expensive that the traditional cubicle office configuration (55/ft² versus $7 to 10/ft²) or $1500 per worker station versus $2000 per worker cubicle. Also, such changes are likely to promote other NEAT-promoting activities in the workplace, which include holding meetings and phone conferencing while walking, celebrating birthdays with “tune-for-day” rather than cake and having stretch bands and yoga stretching as a group dynamic to start each workday. Studies are urgently needed to assess cost-effectiveness and whether productivity improves with such interventions as subjective reporting suggests.

If occupation is the principal determinant of NEAT in adults and represents an efficient means of promoting NEAT in a population, we should also examine the school as a NEAT-promoting environment for children. Childhood obesity is at its highest level globally and for the first time obesity-associated metabolic complications are becoming commonplace in children. Here, we would envisage redesigning the learning environment. Several concepts could be explored; mentored walk to school programs have been successfully trialed, school buses could park 1 mile from the school, the classroom could be engineered to be filled with
treadmill desks, students could use portable data storage tools to listen to a lesson-associated Shakespeare sonnet while walking in the school corridor, classes could be held using advanced communications where a teacher interacts with her students as the student shoots basketball hoops, hockey pucks, or walks on a track, video linking could be aligned with tablet-format personal computers so that the “black board” becomes portable and dynamic. These approaches will necessitate broad-based collaboration and extensive validation that includes measures of attentiveness and school grades. However, the Damocles sword that hangs over our weight-expanding youth merits such endeavor.

The leisure time environment is also subject to redesign including tools that promote activity in the home (such as an alarm clock that starts the bedroom treadmill), feature-enhanced video gaming that promotes movement while gaming and televisions that can only switch-on when the interlaced treadmill is in use. Perhaps movie theaters and airports will have walk-and-watch and walk-and-wait platforms. The opportunities are wide ranging but also include the office environment described above because a greater proportion of the workforce is projected to work from home (www.dol.gov).

It might be viewed as far-fetched and expensive to design environments to promote NEAT living. However, technological capability exists that makes this immediately possible. Moreover, the fiscal and health consequences of obesity may render it cost-effective and health-effective to re-examine sedentary living as the norm. We suggest resource allocation to examine the real-life feasibility of such interventions.

**Conclusion**

In conclusion, NEAT is varies by up to 2000 kcal per day between people of similar size in part because of the substantial variation in the amount of activity that they perform. Obesity is associated with low NEAT; obese individuals stand and ambulate for 2.5 hours per day less than lean sedentary controls. Because walking even at slow velocities is highly exothermic, the NEAT deficit in obesity is likely to be energetically important. It is evident that both biological and, overwhelming environmental influences facilitated a seated lifestyle. Because of the enormity of the problem of obesity in society and because of the magnitude of the NEAT-deficit, we suggest designing and evaluating both, personal behavioral approaches and re-engineered environments to promote active life.

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**References**

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